Clinical Biochemistry News

ACBI

ACB

April 2023

Newsletter of the Association of Clinical Biochemists in Ireland

and the Association for Clinical Biochemistry and Laboratory Medicine (Republic of Ireland Region)

Mater Misericordiae Hospital, Dublin. The 45th ACBI Annual Conference will take place in the hospital's Pillar Centre October 20th-21st 2023

Contents

Editors: Dr. Martin Healy; Dr. Peadar McGing

Message from the President of the Association of Clinical Biochemists in Ireland

Dr. Jennifer Brady

Our new website went live just before Christmas. I hope you have had the opportunity to explore its content and members area. We will be adding to the content going forward with the aim that the website is your primary resource for all information relating to the ACBI and activities. If you have a new publication, relevant news item or job vacancy, please email them to webmaster@acbi.ie for upload to the website.

A recent addition to the website was a news item about a publication from the Covit-D consortium, a group of leading clinicians, scientists and academics from across Ireland, including Clinical Biochemists Dr. Martin Healy and Dr. Paula O'Shea. The paper is a really interesting read and outlines the increased risk of worse outcomes in patients with Sars-CoV-2 and low serum 25(OH)vitamin D. Congratulations to Martin and Paula on this publication. To read the paper, go to the members' publications area of the website.

I am delighted to say that the website CPD module is now operational. You can record your CPD activities, make notes and upload programmes, certificates etc. I would really encourage you all to use this resource to record your CPD activities going forward. Of course, this will become mandatory when our CORU registration board opens, although unfortunately I have no update on the timeline for this. An overview of the CPD scheme and credit allocation guidelines can be found as a pdf file at the bottom of the New Entrants page in the members' area of the website.

Preparations are well under way for our annual conference, which is being held this year at The Pillar Room at the Mater Hospital on October 20th and 21st. It was great to see such an enthusiastic response from most hospitals to form the conference committee, chaired by Dr. Paula O'Shea. This year's themes include Nutrition, Toxicology, Diabetes and Endocrinology and Management. We hope to see as many of you there as possible and please spread the word to colleagues who might be interested in joining us. We will be using our new website to manage registrations, abstract submissions and all conference information, so please keep an eye on the site as well as social media (Twitter **@ACBIrl**) for updates.

Prior to that, there are a number of exciting events taking place that may be of interest to our members:

- UKMedLab23 is taking place in Leeds on June 13th and 14th. The ACB Republic of Ireland region committee is organising a scientific session to celebrate the 70th anniversary of the ACB. ACBI members Drs. Peadar McGing, Joe Duffy and Graham Lee are among the speakers in what promises to be an exciting conference.
- The ISIMD Spring Meeting is taking place on 28th April as a virtual event. The ISIMD programme is always of great interest, bringing together experts in the field of inherited metabolic disorders. While there are specialised metabolic services in the Mater Hospital and CHI at Temple St., patients with an inherited metabolic disease can present anywhere and at any age. Therefore, it is important that we are aware of them, that we know the red flags in biochemistry results and how to go about investigating them further.
- Worldlab-EuroMedLab, taking place in Rome from 21st-25th May, has a very full programme with a number of interesting satellite meetings relating to paediatric laboratory medicine (a hybrid meeting), clinical mass spectrometry and point-of-care testing.

Don't forget that a number of ACBI bursaries are available to support members to attend these and other relevant meetings. Get applications in as soon as possible so that they can be considered by Council. Full details and an application form can be found in the members' area of the website. If you are at a meeting, presenting a poster or giving a talk, let our membership know by tagging **@ACBIrl** on your social media posts or writing a piece for our newsletter.

April 19th is HSCP Day this year. The HSE HSCP office has confirmed that the theme this year is 'HSCP-Moving Forward Together'. Clinical Biochemists are one of 26 health and social care professions represented by the HSCP office. Among other functions the office supports professional CPD and I have attended a number of meetings and workshops with the HSCP office on this topic with more scheduled. While Clinical Biochemists are small in number, our role in healthcare is no less important than any other profession, particularly as the Sláintecare programme moves forward enhancing care closer to the patient. The focus on care in the community leads to challenges relating to near-patient testing and

providing laboratory services for chronic disease management that will require our input and expertise. HSCP Day is therefore a great opportunity to recognise and promote the role of the Clinical Biochemist. We have emailed members about this and encouraged everyone to get involved.

As always, there are plenty of opportunities for our members to get involved in the profession both at national and European levels, with ongoing vacancies on EFLM and IFCC committees. Two of particular relevance are the EFLM Task Force 'Direct-to-Consumer Testing and the EFLM Task Force 'Preparation of Labs for Emergencies'. These are very topical and important subjects to which we must lend our expertise in the interests of patient safety. In both cases we are looking for a Clinical Biochemist to represent the ACBI. No specific experience is required and for the latter task force, I think we all have gained plentiful experience dealing with emergencies over the last few years! I strongly encourage members to put their names forward for these groups. It provides excellent experience being on a committee; you can input your ideas and experience, network with and learn from your colleagues in other countries, as well as being a great addition to your CV.

Don't forget that the ACBI mentoring programme for Clinical Biochemists is now available; information is available in the members' area of the website. Please avail of it if you would like support with your career progression and also get in touch if you are interested in becoming a mentor.

Finally, I hope to see as many of our Clinical Biochemist members as possible at our AGM on April 26th. This will be an in person event at the Mater Hospital, with virtual attendance a possibility for those who cannot travel to Dublin. Nomination forms for secretary and vice–president have been distributed to eligible members. Please consider putting yourself forward for these roles, which are vital to the continued success of the organisation.

Dr Jennifer Brady, ACBI President.

Recent Reviews of Interest

Artificial Intelligence (AI), Machine Learning, Big Data, alone or combined, will have critical roles in the clinical laboratories of the future. Links below give a flavour.

Artificial intelligence: is it the right time for clinical laboratories?
Padoan A, Plebani M. Clin Chem Lab Med. 2022 Oct 24;60(12):1859-1861. doi: 10.1515/cclm-2022-1015. Print 2022 Nov 25

Where is laboratory medicine headed in the next decade? Partnership model for efficient integration and adoption of artificial intelligence into medical laboratories.
Carobene A, Cabitza F, Bernardini S, Gopalan R, Lennerz JK, Weir C, Cadamuro J. Clin Chem Lab Med. 2022 Nov 3;61(4):535-543. doi: 10.1515/cclm-2022-1030. Print 2023 Mar 28

Artificial Intelligence-Based Medical Data Mining.
Zia A, Aziz M, Popa I, Khan SA, Hamedani AF, Asif AR. J Pers Med. 2022 Aug 24;12(9):1359. doi: 10.3390/jpm12091359

Big Data in Laboratory Medicine-FAIR Quality for AI?
Blatter TU, Witte H, Nakas CT, Leichtle AB. Diagnostics (Basel). 2022 Aug 9;12(8):1923. doi: 10.3390/diagnostics12081923

Detailed review of current and future newborn screening developments including AI supported interpretation.

Current State and Innovations in Newborn Screening: Continuing to Do Good and Avoid Harm.
la Marca G, Carling RS, Moat SJ, Yahyaoui R, Ranieri E, Bonham JR, Schielen PCJI. Int J Neonatal Screen. 2023 Mar 17;9(1):15. doi: 10.3390/ijns9010015.

With increasing requests for lipoprotein (a) this concise review outlines its association with heart disease and challenges in its laboratory analysis.

Lipoprotein(a): Insights for the Practicing Clinician.
Telyuk P, Austin D, Luvai A, Zaman A. J Clin Med. 2022 Jun 25;11(13):3673. doi: 10.3390/jcm11133673.

Nuts and their positive influence on glycaemic, lipid and inflammatory markers.

Nuts as a Part of Dietary Strategy to Improve Metabolic Biomarkers: A Narrative Review.
Khalili L, A-Elgadir TME, Mallick AK, El Enshasy HA, Sayyed RZ. Front Nutr. 2022 Mar 29;9:881843. doi: 10.3389/fnut.2022.881843. eCollection 2022.

A Selection of Members' Recent Publications

Instructions on appropriate fasting prior to phlebotomy; effects on patient awareness, preparation, and biochemical parameters.
Andrade NSV, Curtin SN, Masih A, Fitzgibbon B, Herbert K, Gowen M, Lehane M, **Costelloe SJ**. (2023). Diagnosis (Berlin, Germany), Advance online publication. https://doi.org/10.1515/dx-2022-0131

The ability of pGCD59 to predict adverse pregnancy outcomes: a prospective study of non-diabetic pregnant women in Ireland.
Bogdanet D, Castillo MT, Doheny H, Dervan L, Luque-Fernandez MA, Halperin JA, **O'Shea PM**, Dunne FP. (2023). Acta diabetologica, 60(2), 211–223. https://doi.org/10.1007/s00592-022-01983-z

IGF-2 mediated hypoglycemia and the paradox of an apparently benign lesion: a case report & review of the literature.
Crowley MT, Lonergan E, O'Callaghan P, **Joyce CM**, Morita M, Conlon N, O'Halloran DJ. (2022). BMC Endocr Disord. 22(1):262. doi: 10.1186/s12902-022-01175-4

Non-esterified fatty acids (NEFA): sample stability and effect of haemolysis and icterus.
Gillick A, **Brady JJ**. (2022). Clin Chem Lab Med. doi: 10.1515/cclm-2022-0891

Vitamin D Status and Mortality from SARS CoV-2: A Prospective Study of Unvaccinated Caucasian Adults.
Barrett R, Youssef M, Shah I, Ioana J, Lawati AA, Bukhari A, Hegarty S, Cormican LJ, Judge E, Burke CM, Cody C, Feely J, **Hutchinson K**, Tormey W, Neill EO, Shea AO, Connolly M, McCartney DMA, Faul JL. (2022). Nutrients Aug 9;14(16):3252. doi: 10.3390/nu14163252

Comparison of ultrasound with biomarkers to identify large-for-gestational age in women screened for gestational diabetes mellitus.
O'Malley EG, Reynolds CME, **Killalea A, O'Kelly R**, Sheehan SR, Turner MJ. (2022). J Matern Fetal Neonatal Med. Dec;35(25):6306-6311. doi: 10.1080/14767058.2021.1911993. Epub 2021 Apr 28.

Vitamin D: determinants of status, indications for testing and knowledge in a convenience sample of Irish adults
Scully H, Laird E, **Healy M**, Crowley V, Walsh J, McCarroll, K. (2023). Vitamin D: Determinants of status, indications for testing and knowledge in a convenience sample of Irish adults. British Journal of Nutrition, 1-11. doi:10.1017/S0007114523000168

Vitamin D Intake and Status in Ireland - a Narrative Review.
Scully H, McCarroll K, **Healy M**, Walsh J, Laird, E. (2023). Proceedings of the Nutrition Society, 1-31. doi:10.1017/S0029665123002185

Low socioeconomic status predicts vitamin D status in a cross-section of Irish children.
Scully H, Laird E, **Healy M**, Crowley V, Walsh J, McCarroll K. (2022). Journal of Nutritional Science,</i> 11, E61. doi:10.1017/jns.2022.57

Sublethal hyperthermia transiently disrupts Cortisol steroidogenesis in adrenocortical cells.
Mullen N, Donlon PT, Sebek J, Duffy K, Cappiello G, Feely S, Warde KM, Harhen B, Finn DP, **O'Shea PM**, Prakash P, O'Halloran M, Dennedy MC. (2023). Endocrinology Mar 18 doi: 10.1210/endocr/bqad046

Advances in the diagnosis and early management of gestational trophoblastic disease.
Joyce CM, Fitzgerald B, McCarthy TV, Coulter J, O'Donoghue K. (2022). BMJ Med Dec 16;1(1):e000321. doi: 10.1136/bmjmed-2022-000321. eCollection 2022

Medium Chain Acyl-CoA Dehydrogenase Deficiency: 3 years of Newborn Screening.
Howard C, Gorman I, Crushell E, Knerr I, Hughes J, Boruah R, O'Grady L, Elsammak MY, **Brady JJ**, Monavari AA. (2023). Ir Med J Mar 23;116(3):743 PMID: 37010499

Recommendation for the design of stability studies on clinical specimens.
Gomez-Rioja R, Von Meyer A, Cornes M, **Costelloe S**, Vermeersch P, Simundic AM, Nybo M, Baird GS, Kristensen GBB, Cadamuro J; European Federation of Clinical Chemistry; Laboratory Medicine (EFLM) Working Group Preanalytical Phase (WG-PRE). (2023). Clin Chem Lab Med Apr 6. doi: 10.1515/cclm-2023-0221

Abbreviated lipid guidelines for clinical practice : Based on ESC lipid guidelines 2019 and ESC cardiovascular disease prevention in clinical practice guidelines 2021.
Maher V, Gallagher J, Agar R, **Griffin D**, Colwell N, O'Connor P, McAdam B, Tomkin G, Owens D, Ryan M, Tormey W, Durkan M. (2023). Ir J Med Sci Feb 7. doi: 10.1007/s11845-023-03277-x

Association for Clinical Biochemistry and Laboratory Medicine Republic of Ireland Region (ACB RoI Region) Scientific Meeting 3rd February 2023

Reported by Clodagh Kivlehan (St. Vincent's University Hospital, Dublin), Micheál Ryan (University Hospitals Limerick), Alison Bransfield (Cork University Hospital), Carl Talbot (Mater Misericordiae University Hospital, Dublin), Ciara Cunning (Mater Misericordiae University Hospital, Dublin). Edited by Peadar McGing.

The ACB (RoI Region) held its AGM and Scientific Meeting on Friday February 3rd, 2023. The meeting was held via Zoom and a sizeable audience tuned in.

The meeting was opened by Dr Jennifer Brady, Consultant Clinical Biochemist in Children's Hospitals Ireland and the Chair of the ACB RoI region. She welcomed all speakers and delegates, and in particular thanked Dr. Bernie Croal, the President of the ACB, for his support. After her address Carl Talbot, Senior Clinical Biochemist in the Mater Hospital chaired the first session of the day.

Paediatric growth hormone deficiency

Professor Colin Hawkes, Associate Professor of Paediatrics at University College Cork, Adjunct Associate Professor at the University of Pennsylvania and Consultant Paediatric Endocrinologist at Cork University Hospital, delivered the first talk on the day entitled '(Mis)diagnosing paediatric growth hormone deficiency – clinical and biochemical challenges'.

Prof. Colin Hawkes [photo courtesy UCC]

Faltering growth is a paediatric vital sign. It is an important indicator of disease in children and should be investigated appropriately. He provided a succinct summary of the clinical and diagnostic challenges associated with the investigation of short stature in children. He detailed the clinical assessment performed prior to any laboratory testing, how this data influences the laboratory tests that may be requested, and he discussed diagnostic challenges encountered with test selection and interpretation.

To arrive at an accurate diagnosis, the clinician must ensure the correct height measurement is taken and normal variations of growth are considered before any laboratory testing is performed. Professor Hawks demonstrated the different growth phases in a child until adolescence on a chart, showing children generally gain height, weight and head circumference along a particular curve. This may fall off approaching puberty if the timing does not correspond with the average population. He emphasised the significance of taking the skeletal age into account rather than the chronological age because this can profile for a later onset of puberty, adding that a bone age x-ray of the wrist can be used to determine the age of the skeleton.

Clues to pathology can be derived from previous height data points, weight and proportionality. The laboratory can play an important role where pathology is suspected. There is an extensive list of pathological causes of abnormal growth in children, including genetic disorders, skeletal dysplasia, endocrine disorders, nutritional issues, chronic diseases such as anaemia, coeliac disease, liver, renal and cardiac issues, in addition to growth hormone deficiency. Laboratory tests for investigating atypical growth patterns include FBC, ESR, creatinine, electrolytes, albumin, calcium, phosphorus, alkaline phosphatase, TSH, prolactin, LH, FSH, testosterone, oestradiol, IGF -I, IGFBP-3, karyotype, and coeliac screen, all of which can provide valuable information to the clinician.

Unfortunately, there are limitations to growth hormone stimulation testing, including poor specificity and patient- and test-specific variability. Despite a range of potential variables, a target cut-off of 7 ng/mL is used to determine if a test is a pass or fail. The cut-off does not take into account factors such as stress, pubertal stage, BMI, caloric restriction, provocative agents, assay type, all of which can impact the pass rate. Concerningly, Professor Hawks presented findings that ¼ of children with no growth hormone deficiency will be classed as having an insufficient response to the insulin tolerance test. It is recommended that two tests on separate days be used to improve the pass rate. He took us through a survey on what happens in Ireland: 40% perform two stimulation tests on separate days; however, 25% diagnose GH deficiency if peak is not achieved in one of the two tests. 50% only perform one stimulation test. Common stimulants used include glucagon, insulin tolerance testing, arginine, and clonidine. 90% use the threshold of 7 ng/ml.

Professor Hawks provided insight into the clinical and

diagnostic challenges associated with the investigation of short stature in children. He highlighted the need for caution when utilising GH stimulation testing and stated that there is an over diagnosis of GH deficiency. Careful clinical assessment will minimise unnecessary diagnostic testing and multiple GH stimulation tests are advised to overcome poor specificity. He concluded that faltering growth is an important early indicator of disease in children and should be carefully investigated.

Treatment of obesity

Next to speak was Prof. Carel Le Roux, who delivered a very informative presentation on new therapies for the treatment of obesity.

He opened his talk by providing the audience with an explanation that obesity is a chronic disease, as defined by the World Health Organisation ('Obesity is defined as excess or abnormal adipose tissue that causes a deterioration in health')

In addition, he asserted that there is a need to move patients' objectives away from the cultural desire for thinness with a focus on weight loss as a necessary means to halt health deterioration.

Prof. Le Roux referred to the STEP Trials (**S**emaglutide **T**reatment **E**ffect in **P**eople with obesity Trials 1 to 3 and STEP TEENS) trials to provide an evidence base for the effectiveness of Semaglutide (a weekly injectable glucagon-like peptide (GLP)-1 receptor agonist) on weight loss in adult patients, with and without diabetes, and in adolescents.

The STEP 1 trial involved participants that were overweight or obese with related comorbidities, but not diabetes.

Prof. Carel Le Roux [photo courtesy Prof. Le Roux]

This trial revealed an average 14.9% reduction in bodyweight from baseline during 68 weeks of treatment with semaglutide 2.4 mg plus a lifestyle intervention, compared with just a 2.4% reduction in the placebo plus lifestyle intervention group. In total, 86.4% of the semaglutide group lost at least 5% of their bodyweight, and adverse effects were in line with those expected for the medication class.

The STEP 2 trial recruited participants with type 2 diabetes and defined as overweight or obese. It tested the standard approved 1.0 mg dose of semaglutide versus a higher 2.4 mg dose and matched placebos over 68 weeks. Average bodyweight reductions were 9.64%, 6.99%, and 3.42% with semaglutide 2.4 mg, 1.0 mg, and placebo, respectively. The higher dose also achieved slightly better glycaemic control, and reductions in cardiometabolic risk.

The STEP 3 trial involved overweight or obese participants with related comorbidities, but not diabetes. Participants were randomly assigned to receive semaglutide 2.4mg or placebo in addition to intensive behavioural therapy to support them to adopt a healthier lifestyle. The average weight reduction after 68 weeks of treatment with semaglutide was 16% versus 5.7% with placebo. The co-primary endpoint of at least a 5% reduction in bodyweight was met by 86.6% versus 47.6%.

The STEP TEENS trial tested the weight-loss efficacy of semaglutide 2.4 mg in adolescents (aged 12 -17 years). Active treatment was associated with a significant 16.1% reduction in baseline BMI with the placebo associated with a 0.6% increase.

Prof. Le Roux proceeded to provide an insight into the overall treatment strategy that can be adopted for the management of obesity starting with self-directed lifestyle adjustments followed by professionally led lifestyle advice. Pharmacotherapy may be then be required with a further escalation to obesity surgery or combination therapy.

In conclusion to his excellent presentation, Prof. Le Roux highlighted that not all forms of obesity require treatment, but intervention should always aim to result in health gain.

Future of Phamacogenetics

For the final talk of the session the ACB Republic of Ireland region was delighted to welcome Professor Sir Munir Pirmohamed, the NHS Chair of Pharmacogenetics at the University of Liverpool, to speak on the topic of Pharmacogenomics. Sir Munir told the meeting that there is wide variability in drug efficacy – more than 90% of drugs only work in 30 to 50% of people. The variations can be due to pharmacokinetics (absorption, distribution, metabolism and elimination) or pharmacodynamics (ion channels, receptors, enzymes and nucleic acids). As many drugs are eliminated renally chronic kidney disease has a large impact on the amount of drug which remains in the body post dose, for example dosage of Aztreonam

should be halved in patients with eGFR between 10 and 30 mL/min/1.73m^2.

Professor Sir Munir Pirmohamed
[photo courtesy University of Liverpool]

The area of pharmacogenomics works to identify genomic variation in order to best select the appropriate drug/dosage combination for a particular patient or group of patients. The areas of interest are: metabolic phenotyping, PCR testing of single variants, genome-wide association tests, exome sequencing and whole genome sequencing. In studies involving the US, UK, Australia, Canada, Estonia, Netherlands and Qatar, the proportion of the studied population carrying at least one actionable genotype or diplotype ranged from 91.4 to 99.8%.

Clopidogrel is a widely-prescribed anticoagulant which is metabolised via the cytochrome P-450 pathway. Polymorphisms in this pathway are common and will affect certain groups of patients more than others. In 2021 Bristol-Myers Squibb Co and Sanofi SA were ordered to pay more than $834 million to the state of Hawaii for failing to warn non-white patients of the health risks of use of Clopidogrel.

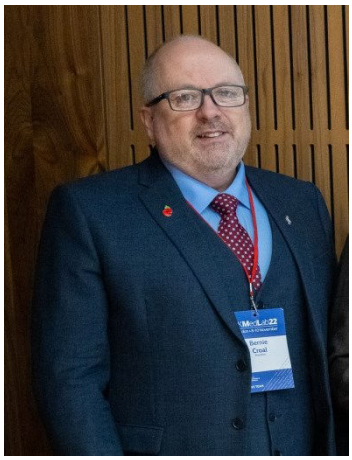
The Human Leucocyte Antigens (HLA) are involved in the pathogenesis of immune-mediated adverse drug reactions; more than 200 genes are involved in their coding. A HLA Allele Panel test has been developed which can genotype for multiple HLA alleles and can give results in ≈ 48 hours. This has the potential to identify the relevant HLA variants ahead of prescription, thus avoiding or limiting adverse reactions while maximising the therapeutic benefit of a drug.

Finally we heard about the PREPARE (Pre-emptive Pharmacogenomic testing for preventing Adverse Drug Reactions) initiative which is a Europe-wide collaboration to use pharmacogenomics guided prescribing. This was a comprehensive and thought-provoking talk from a leader in the field of pharmacogenomics and was greatly enjoyed by the attendees.

Following these three engaging lectures there was a break for DIY tea or coffee. The meeting then resumed with the second session, this time with Dr. Heloise Tarrant, Acting Principal Biochemist in St. Vincent's Hospital as Chair.

Build Back with Labs

Session 2 of the meeting began with a talk by Dr. Bernie Croal, President of the Association for Clinical Biochemistry and Laboratory Medicine who presented his talk 'Build back with Labs'. The COVID-19 epidemic significantly impacted the healthcare service in the UK and Dr Croal's presentation emphasised the importance of the laboratory service role in the recovery of healthcare delivery. He talked about the dramatic impact of the pandemic on the delivery of laboratory services where non-essential work was postponed to focus resources on dealing with the pandemic. Reduced patient interaction in primary and secondary care as a result of lockdown led to large backlogs in a number of areas.



Dr. Bernie Croal [Photo: Alastair Fyfe]

Dr. Croal highlighted the use of Demand Optimisation in the Laboratory as a way to keep patient pathways working as efficiently as possible so that labs may contribute to the recovery of the healthcare service. He discussed the collaborative efforts that the ACB, IBMS, RCPath and other NHS stakeholders are making in addressing issues around implementation of effective Demand Optimisation. Dr. Croal is the Chair for the National Demand Optimisation Group (NDOG) a Scottish government commission group aimed at developing a programme to reduce unwarranted variation in the delivery of healthcare thus leading to a more efficient use of NHS resources. He demonstrated how pathology specimens may be used as a robust marker of healthcare activity through the use of NDOG's lab activity dashboard. The potential benefits from this collection and analysis of data through the dashboard include the ability to identify gaps in cancer or chronic disease pathways, reducing unwarranted lab

variation and helping in the allocation of laboratory resources.

Dr. Croal addressed a number of obstacles to 'Build Back with Labs' within the UK. Supply chain issues have been a challenge for many laboratories in the UK since Brexit with shortage of consumables, reagents and blood tubes providing additional problems for labs to mitigate. He also points to direct to consumer testing as an emerging market that may have adverse consequences for the GP and laboratory services if they have to follow up on any abnormal results.

Leading Effective Change

The final talk of the meeting was by Tina Joyce, titled "Leading effective Change – in the Laboratory and Beyond". Change as we know is constant and during the talk Tina informed us of the different types of change and the many external drivers of change in healthcare including political, economic, social, technological, legal, and environmental.

The talk highlighted how people react differently to change and the importance of adapting and having the tools available for understanding the impact of change. Tina discussed the importance of understanding why change is needed, having a plan in place to implement change and figuring out how to embed change into the culture. The presentation reminded us that change often affects whole ecosystems due to the many interconnections within the workplace and discussed how people accept change differently including those that adapt early, those that look to leaders for reassurance and those that are sceptical and resist the change.

Tina outlined the different ways of managing change including from the "top down" in which resistance might be ignored, or from the "bottom up" in which staff at all levels are communicated with, have meaningful involvement and are crucial to the outcome. As a leader, we must understand why people resist change and that people often want to be involved and give their opinion. To lead a change, it is important to understand others and their core needs and motivation at work. This was nicely summarised by the acronym "ABC" which stands for *autonomy* (the need to have control over one's work life), *belonging* (the need to be connected) and *contribution* (the need to have a valuable role in healthcare). Leaders must be compassionate, attending, understanding, empathetic and helpful but above all else leaders themselves must be in a good position both physically and mentally to help others.

Close of meeting.

There was time for some audience questions to Tina Joyce before session chair Heloise Tarrant handed over to Dr. Brady for closing remarks. Jennifer thanked all those involved in what had been an excellent morning's science. That concluded the scientific meeting and all could turn off their zoom links and relax over lunch, wherever in the country they were.

After lunch ACB members attended the region's AGM, where Alison Bransfield became the new ACB RoI region chair, and Ciara Cunning took up the role of secretary/treasurer.

Condolences

Condolences are offered to the family and friends of Dr. Rosemarie Freaney, retired Principal Clinical Biochemist, who passed away very recently. Rosemarie ran the Metabolic Laboratory in St. Vincent's Hospital, Elm Park, and was a pioneer in the field of bone biochemistry, particularly of Vitamin D analysis. A full obituary will be carried in our next issue. The photos below are of Rosemarie attending the ACBI Annual Conference in the mid-eighties

The ACBI also wishes to offer condolences to former ACBI member Dr. Selby Nesbitt on the recent death of his wife Paddy (Patricia).


RCPath Building

UKMedLab22: The Royal College of Pathologists London, UK

A report by Dr. Peadar McGing

My first ACB annual conference was Focus'86 in Glasgow. On Tuesday the 8th of November I headed off to London to UKMedLab22 for what I presumed might well be my last (but then I was invited to speak at UKMedLab23).

In 1986 my poster (*A New CK Isoenzyme?*) fitted in my briefcase, as in those days everything was printed, in very large font, on A4 pages which had to be individually affixed to the poster board. In 2022 my entire poster was on one A0 sheet rolled up in a special plastic carry-case. The downside of my modern poster was that it had to go as 'Outsize Baggage' in the hold — its non-appearance on either the regular carousel or the Zone A Outsize Luggage belt led to an anxious 20 minutes or so. On foot of my inquiry, a blockage was found in the system and my poster case was located, freed, and hand delivered. Phew!!

UKMedLab22 was a return to an in-person event, and I really enjoyed that. The 2022 meeting was a two-day conference with Training Days and an Audit meeting on the day following the main conference. Back in 1986 the conference was four days plus the training day, but even with the shorter duration in 2022, it was difficult for people to get away from their labs. Most unfortunately, a threatened tube strike caused major difficulties (only cancelled at the last minute). The Training Day was moved at short notice from Monday to Thursday, and with no zoom option available, the two trainees from Ireland were unable to change their arrangements and so could not attend.

I had booked a one-day registration for Day 2 (Wednesday), that being the day my poster was on display. As the meeting was being held in the new RCPath building, and I had other business there also, I walked to 6 Alie Street and headed for the meeting registration desk. I gave my name, and while the young man was checking his list, I heard a voice from an adjacent desk: Ah, Peadar, you're ACBI secretary, aren't you". A bit of ACBI/ACB business later, it being lunchtime, I made my contribution to food waste reduction by joining in the light buffet and enjoying some networking.

On Wednesday morning, with the tube strike now deferred, I enjoyed a straightforward trip to Alie Street, happily shared with a fellow delegate I happened to meet at Earls Court station. A quick change from runners to shoes beside the basement cloakroom, up to the 6th floor to stick up my poster, and then back down to the Elizabeth Room on the 1st floor for the Impact Award Lecture. This is a new innovation, and a really excellent one at that.

Impact Award - Alkaptonuria

The Impact Award was introduced as 'an opportunity for ACB Members working in Laboratory Medicine to showcase and be recognised for an initiative they have delivered, either as an individual or group, which has resulted in positive change to a service'. The award was made to Ranganath Lakshminarayan and his colleagues. They presented an absolutely fascinating award lecture: *The National Alkaptonuria Centre (NAC) - making a difference through innovation and excellence*.

Professor Lakshminarayan opened the presentation by giving us details of alkaptonuria (AKU) and, in particular, of the clinical manifestation, ochronosis, in which pigment deposition causes hardening of tissues. Symptoms and test measurements vary between patients, and to help concentrate and develop multi-disciplinary expertise, he set up the Robert Gregory National Alkaptonuria Centre, based at the University of Liverpool. Patients referred to the centre undergo four days of baseline testing, with three follow up visits also scheduled. Two important factors in the assessment and treatment of AKU patients are the alkaponuria severity score index (AKUSSI), which he developed, and the availability on a trial basis of a new drug, nitisinone.


ACB President Bernie Croal with Impact Award winners Nicolas Sireau, Ranganath Lakshminarayan, and James Gallagher, with ACB President-elect Kath Hayden [Photo: Alastair Fyfe.]

The development of that drug was outlined by Professor James Gallagher. He described the fascinating story of how nitisinone was originally developed as a weed-killer but subsequently found use in the treatment of tyrosinaemia type 1. He told us how someone in their team thought it might work for AKU, and mouse models gave strong support. It is currently in clinical trials and looks very promising. Continuing the sideways development of that drug, it is now being looked at for a

much more common condition – malaria – in work the centre is doing with the Tropical Diseases Unit in Liverpool.

We next heard from Nicholas (Nick) Sireau, who is CEO of the AKU Society and also the father of two children with AKU. He gave an insight into that parental role and how, in rolling out publicity about the disease, they found many more undiagnosed patients who are now being treated at the Centre. I found it particularly interesting that when trying to raise funds they avoided the clinical term alkaptonuria and instead opted for the plea 'please help my black bone disease'. This fascinating story of collaboration between affected individuals and their families, clinicians, and scientists is now being taken up by other rare disease groups; to help them not have to re-invent the wheel, the group has authored a publication 'The Patient Group Handbook'.

This group was truly a worthy winner of ACB's newest award. Their award lecture covered basic biochemistry, clinical symptoms, and treatment, as well as the drive and vision to achieve so much. A valuable lesson too is that in working to understand a rare disease and to improve the lot of those suffering from that condition, they have opened up windows of knowledge on other conditions and opened doors to potential treatment for many more patients.

Innovations in Cancer

Those who know me will not be surprised that the parallel session I chose was 'Innovations in Cancer', though the session 'Maintaining quality in the changing face of service delivery' also looked interesting.

Circulating Tumour DNA

In time I believe the measurement of circulating molecular markers will replace conventional serum protein markers, so I was very interested in the opening presentation of this session, *Clinical utility of circulating tumour DNA in early stage breast cancer*. Isaac Garcia-Murillas, from the Institute of Cancer Research, gave a very good outline of the difficulties with circulating tumour DNA (ctDNA) analysis and also the benefits which are starting to come from this as yet experimental test.

Section of audience at UKMedLab22 cancer session (spot the author). Photo: Alastair Fyfe

The circulating tumour DNA represents a minority component of total circulating DNA and is a small molecule which is difficult to work with. Molecular tools for ctDNA analysis need to balance sensitivity with practicality and basic techniques suffer from low sensitivity. Distinguishing relevant from non-tumour related mutations also presents significant challenges. Prospective clinical trials are now running to assess whether detection of ctDNA can improve patient outcomes, and early results do give grounds for some optimism.

This technology does have potential to bring about new treatment paradigms for breast cancer, with ongoing treatment initiated on the basis of molecular relapse before symptomatic but incurable metastatic disease develops.

Genomic Diagnostics

A similar theme was the subject of *Genomic Innovations in Clinical Cancer Diagnostics*, delivered by Michael Hubank, also from the Institute of Cancer Research. Targeted therapies are more successful and less wasteful, and they benefit patients, clinicians, and drug developers. At the end of 2021 there were more than 100 FDA-approved drugs with companion molecular biomarkers and over 60 biomarkers that indicate drug applicability.

One important technique is whole genome sequencing (WGS), and we were told how this can be very useful in rare disease diagnosis. It can also help with some cancers, and current NHS England test indications for WGS include sarcoma, AML, and ALL, among others, with specific pilot studies for triple-negative breast cancer and high-grade ovarian cancer. [Full details at https://www.england.nhs.uk/publication/national-genomic-test-directories/].

RNA Fusion Testing was also discussed, a technique that is very useful in sarcoma testing. In concluding his talk he made a particular point that although patients want all the data arising from their tests to be used for research into their cancers the UK government routinely brings up blocking issues relating to GDPR etc.

Man Health

Masood Moghul, a neurology registrar from the Royal Marsden Hospital with a special interest in prostate cancer, gave a very interesting talk on the Man Van Project. To quote from the Royal Marsden website, 'The Man Van is a mobile health clinic that offers free health checks for men in a private and relaxed environment. It aims to identify and address undiagnosed health conditions and facilitate earlier diagnosis of urological cancers'. They engage with the local community in a nurse-led welcoming environment aimed at individuals with no symptoms of disease. Tests include blood pressure and blood tests, including PSA. The group is currently validating a POCT system to get a 15-minute TAT on the blood tests. In answer to a question on PSA screening, Dr. Moghul said the argument is changing as

more long-term evidence becomes available from the big trials, but more particularly as the follow-up to a raised PSA is changing. MRI has replaced biopsy in many cases, and morbidity associated with follow-up testing has been significantly reduced.

Photo courtesy The Royal Marsden Hospital

Myeloma

The session finished with Dr. Kevin Boyd of the Royal Marsden Hospital updating us on myeloma with his lecture, *Myeloma: Intersection with Biochemistry and Current Treatment Innovations."* He informed us that myeloma is neither rare nor common, with about 5,000 new cases a year in the U.K.

While most bone change in cancer is sclerotic, myeloma bone damage is lytic. Myeloma is a malignancy of plasma cells, which are terminally differentiated B cells. The plasma cell's job is to produce antibodies, but in myeloma there is overproduction of one antibody (paraprotein). A side effect of this is that nearly all patients have immune paresis at presentation because of the suppression of normal immunoglobulins.

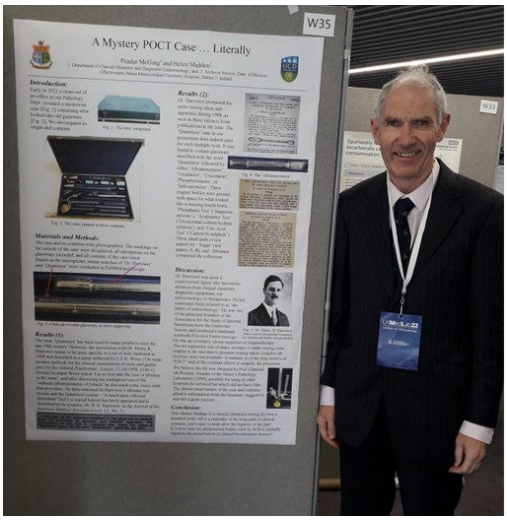
Dr. Kevin Boyd. [Photo: Alastair Fyfe]

About 85% of myeloma patients produce intact paraprotein, with the other 15% mainly producing light chains. The free light chain myelomas carry a worse prognosis, especially lambda myelomas. Kevin informed us of how free light chain testing has largely replaced quantitation of Bence Jones Proteinuria (BJP), revolutionising monitoring of these patients, though some drug trials still require BJP measurement. For paraprotein testing, the long established protein electrophoresis is the method of choice routinely, but it is not sensitive enough when looking at minimal residual disease (MRD) checking / treatment. Mass Spectrometry is currently being trialled in an attempt to achieve the required sensitivity for MRD testing.

The good news on the treatment side is that many improvements have been seen in the past ten years or so, mainly due to newer drugs. Dr. Boyd concluded his talk by telling us that the current big leap in myeloma therapy is with the anti-BCMA drugs. BCMA stands for B-Cell Maturation Antigen, which is a protein found on the surface of most myeloma cells and normal plasma cells. It isn't found on many other types of cells, so it's is a good target for myeloma treatments. Though much more difficult than other therapies, CAR-T cell therapy is the one he believes will probably be the best treatment (CAR = Chimeric Antigen Receptor).

Lunch and Posters

Lunch beckoned, so I headed to the sixth floor where I filled my plate from the lunch buffet and walked the few short steps to my poster. As a slightly older poster presenter, it was probably appropriate that my poster concerned an aspect of the history of clinical biochemistry. The poster, entitled *A Mystery POCT Case … Literally* reported on an actual carry case recently found at the back of a cupboard by the new occupant of a Pathology office. The case, which was thankfully passed to the hospital archivist (my co-author), contained glassware, reagents, and paper strips for various biochemistry tests including albumin, protein, sugar, and others.



I was able to trace the kit to 1909, when it was very likely owned by Professor Edmond McWeeney, the first whole-time Professor of Pathology in Ireland and the founder in 1890 of the Mater Pathology Laboratory. The kit was designed and marketed by Dr. Henry R. Harrower (photo shown on the poster). He subsequently enjoyed much more success in endocrinology and therapeutics and is sometimes referred to as 'the father of endocrinology'.

Award Lecture — Green Labs

After lunch the International Award Lecture was given by Prof. Tomris Ozben. Prof. Ozben is the President of EFLM and President-elect of IFCC and was a guest at our ACBI conference last November. Her talk was entitled *Implementation of sustainable practices in medical laboratories; switching clinical laboratories to Green Labs*. She began by pointing out that so much opportunity to recycle is wasted in today's society. About 86% of plastics are not recycled; 30% of food is wasted, and this also generates unnecessary CO_2 emissions. She informed us that 'Green' is about environmental protection and health, while 'Sustainable' is also about economic factors. The 3 Ps of sustainability refer to People, Profit, and Planet (covering social, economy, and environment, respectively). Laboratories in general have been shown to be leading contributors to waste and CO2 emissions. EFLM has a Task Force on Green Labs which is trying to address the need to be more green while at the same time providing high quality services for patients. At the time of this lecture, there were 49 National Society members in the Task Force and training for the 49 National Society representatives is underway.

Prof. Ozben outlined the Green Labs certification process and its benefits. Green Lab management involves both technical and behavioural changes. Technical changes give more resource savings but are generally more expensive. Examples include improving ventilation, increasing pipe insulation, replacing equipment with newer energy-saving models, replacing old bulbs with LED lights, etc. Behavioural changes are more gradual and require laboratory staff to change their behaviour to help save resources. Examples she gave include closing laminar flow, using less water, reducing waste (e.g., through the procurement process), turning off lamps, computers and equipment when not in use, and sending less emails.

International Award winner Tomris Ozben with President -elect Kath Hayden [Photo: Alastair Fyfe.]

Making the laboratory sustainable and green may not be achievable immediately, but, she told us, 'the important thing is to make the decision and start somewhere'.

Renal Medicine

After a short break to refresh body and mind, there was just time to make it to the Renal Medicine session in the Grosvenor Room. My choice of this session had nothing to do with the room name and my fond remembrance of student days in a flat in Grosvenor Square, but rather that one of the lectures was about EQA and I was also interested in the AKI reporting process.

Unwarranted Variation

The session opened with Dr. Martin Myers telling us about Unwarranted Variation in AKI Reporting. Martin is the main man in the GIRFT programme (Getting It Right First Time). Martin and I were on ACB committies together and it was great to have a little chat with him and to hear more of this very important work. His group's investigations into UK reporting of AKI warnings showed a 4- to 5-fold variation, with no good reason for the variation; he defined a good reason as one that he believed. They also found that 30% of AKI algorithms used in labs were the wrong algorithm, mainly from one supplier (now sorted). Of key importance, he pointed out a lack of monitoring whether results were clinically correct. Laboratory scientists need to encourage clinicians to have discussions with the laboratory, including to review clinical correlation of laboratory results.

Dr. Martin Myers. [Photo: Alastair Fyfe]

AKI Audit

AKI costs the NHS about five million pounds a year. Anna Barton, Principal Clinical Biochemist at the Royal Cornwall Hospital, in her presentation *AKI Past, Present and Future* reported on the UK's 2021 National AKI Audit. They got 98 responses from 91 labs; 50% were Roche instruments. During her talk she reported the full survey and all the answers they received. The group made ten recommendations, one of which has been modified since. The recommendations were fully endorsed by ACB, UKNEQAS, GIRFT, and the UK Kidney Association (UKKA). They include strong recommendation to use enzymatic creatinine, participate in AKI EQA, LIMS algorithm must not be editable, and there must be local processes to alert clinical teams to new Stage 2 and 3. Anna and her colleagues are finalising a paper for the Annals, so keep a look out for that later this year.

EQA for AKI

Next up was Dr. Rachel Marrington, Consultant Clinical Scientist and Deputy Director at Birmingham Quality (UK NEQAS). Her talk stressed The necessity of EQA in Clinical Decision Pathways. Because of the nature of the AKI

algorithm, any bias at low concentrations can have a significant impact on the RV ratio and consequently on the AKI stage (remember that creatinine is the denominator). UKNEQAS started its EQA scheme for AKI in July 2021. Participants receive three specimens for creatinine and need to log the AKI 'patient' into their LIMS (with dates and times entered correctly).

Time to go

An unfortunate side effect of the rail strike was that I had to book a bus to the airport instead of the train, which resulted in my leaving earlier than I would have liked. I missed the chance to chat and discuss EQA with Rachel after that renal session, and I also missed the final talk.

The ACB national meeting is always worth attending. I hope this report will give you a flavour of the event and encourage more of you to attend this year's conference, which takes place in Leeds in June. Bursaries may be available from ACB and from ACBI to cover part of your expenses.

Poster viewing [Photo: Peadar McGing]

Award of Fellowship of the Association of Clinical Biochemistry and Laboratory Medicine (ACB)

Congratulations to Dr. Peadar McGing who was recently made a Fellow of the ACB. The citation reads:

"The award of Fellow of the Association has been created to recognize individuals who have made an outstanding contribution to the practice of clinical biochemistry and laboratory medicine."

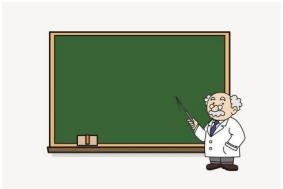
Peadar's extensive contributions to the profession were outlined in the submission to the ACB prior to his being awarded the Fellowship. With 38 years as a member of the ACB he was a long-time member of the ACB Republic of Ireland Regional Committee and held several prominent positions including Chairman and Treasurer.

His contributions to education are numerous, including establishing the MRCPath/FRCPath Training Group for the Republic. He has lectured on many courses, most recently the UCD MSc in Clinical Diagnostics and Biochemistry programme and the EFLM Syllabus Course. Peadar continues to be involved in the education of up-and-coming Clinical Biochemists.

Over the years Peadar established several laboratory services in the Mater Hospital, including tumour markers, cardiac markers and atypical fluids and edited and authored ACBI Guideline Booklets on each of these.

He has contributed articles to professional journals, medical newspapers and the lay press and has been assistant editor of Clinical Biochemistry News for over 30 years (and has been a driving force behind that publication).

Upcoming Meetings and Educational Resources



45th Annual ACBI Conference. Pillar Room. Mater Misericordiae University Hospital. October 20th - 21st 2023. Themes: Toxicology, Nutrition, Diabetes and Endocrinology, Management. Updates as they happen on the ACBI website.

UKMedLab23, Leeds, 12th - 14th June 2023 70th Anniversary Meeting. Biochemistry Training Day 12th June. Presentations will be made from all ACB regions including the Republic of Ireland. Brendan Byrne will chair the RoI session beginning at 9.00 am on the 14th with talks from MJ Duffy, Peadar McGing and Graham Lee. Topics being presented and further information about the meeting can be found here.

WORLDLAB:EUROMEDLAB. 25th International and European Congress of Clinical Chemistry and Laboratory Medicine, Rome, Italy, 21st - 25th May 2023. Full details here.

Intelligent Medicine: AI in Medicine, Basel Switzerland, 13th - 14th September. For the latest developments in artificial intelligence, big data etc. Web page here.

The Royal Osteoporosis Society: Osteoporosis Conference 2023 (Equity in Bone Health). University of Manchester, 13th - 14th September, 2023. Wide ranging conference covering clinical and biochemical aspects of osteoporosis. Information here.

A freely available clinical chemistry textbook can be found here. The work is licensed under a Creative Commons 4.0 - Atribution CC BY NC ND
13 Chapters. Covers the fundamentals with good graphics and includes case studies at the end of each chapter.

Another free textbook can be found here. The work is also licensed under a Creative Commons 4.0 - Atribution. Shortish chapters. 38 in all. Chapters can be accessed directly by hyperlink. Covers topics not included above.

Webinars/Editorials/Reports

Members of the ACBI, through its association with the EFLM, have access to an array of educational materials generated by the Federation. These include free upcoming webinars e.g. *Cushing syndrome and its biological work up, Machine learning based clinical decision support using laboratory data, and Nutrition and biochemistry* amongst many others.

The American Heart Association have pledged $250 million to create a Food Is Medicine Research Initiative. This arises from the realisation that many diseases, and in particular, cardiovascular disease and diabetes, have a strong connection with unhealthy, low quality diets. An editorial in Nature Medicine *(Food as Medicine: translating the evidence)* looks at several ways of incorporating food therapy into treatment and preventive pathways.

How are laboratory services impacted in areas of conflict? With an estimated 110 world-wide conflicts ongoing what can be done to maintain adequate diagnostic testing in these regions? A CCLM editorial addresses this issue and highlights several ways that services can be maintained in very difficult circumstances.

The worst of the Covid-19 pandemic appears to be past us and many countries are downgrading emergency measures. A growing number of infectious disease experts, however, warn against complacency. Pandemic readiness remains vital. This editorial emphasises future preparedness. The authors point out that clinical laboratories must be ready to handle increased diagnostic workloads.

Lifespan is increasing every decade but despite this our years in a healthy, disease free state are not keeping pace. Frailty is a major component of this. It is a largely age-related clinical syndrome characterised by the physiological decline in several body systems resulting in susceptibility to a host of morbidities including falls, increased hospitalisations and cognitive difficulties. A comprehensive review of frailty can be found here. For an Irish perspective see these two Irish Longitudinal Study on Ageing (TILDA) reports here and here.

International Federation of Clinical Chemistry (IFCC) and European Federation of Laboratory Medicine (EFLM) Update

Compiled by Alison Bransfield

IFCC/EFLM Committee opportunities

There are no Committee opportunities available at present. Please see www.eflm.eu for any updates

CCLM

- There is a new issue of 'Clinical Chemistry and Laboratory Medicine (CCLM)' available online from De Gruyter Online: Volume 61, Issue 4. This can be accessed through your EFLM Academy logon

IFCC/EFLM News

- The current issue of EuroLabNews, the bi-monthly EFLM newsletter, is available online.
- The EFLM Task-Force Green Labs has developed the EFLM Guidelines for Green and Sustainable Medical Laboratories" which can be accessed here

The calendar of upcoming events may be accessed here

EFLM Academy

- Please note that EFLM Academy membership includes access to CLSI documents
- The new EFLM e-learning academy has now launched and is a comprehensive educational resource
- The current issue of IFCC News is available online
- The current issue of eJIFCC Volume 33-no4 is available online

Upcoming Meetings/Events

EFLM

- EFLM has established a series of webinars covering different diseases and their diagnoses using biomarkers. The leaflet is available here 2023-EFLM-Lessons-Immunochemistry
- EFLM live webinars are available here: https://www.eflmelearning.eu/site/live-webinar
- Previous webinars available at https://www.eflm-elearning.eu/site/on-demand-webinar
- AACC Learning Lab is now available free of charge. For details see https://area9lyceum.com/laboratorymedicine/
- EFLM has established the Task-Force "Green Labs". For more information click here
- The EFLM Task-Group on Chronic Kidney Disease has published a position statement on the use of the race-free CKD-EPI equation. It may be accessed here
- XXV IFCC-EFLM WORLDLAB EUROMEDLAB ROMA 2023 **May 21st – May 25th 2023** https://2023roma.org/

Webinars

- IFCC is looking for volunteers to present webinars; contact ACBI president for information if interested
- EFLM Green Labs presentations are available and will be uploaded to the new ACBI website

Meetings

XXV IFCC WORLDLAB Roma May 21-25, 2023 http://2023roma.org. Satellite meetings have now been announced, including paediatric laboratory medicine and mass spectrometry

5th Symposium CELME 2023 Cutting Edge of Laboratory Medicine in Europe Oct 12th – 13th 2023 http://www.celme2023.cz/programme.php

IFCC/EFLM websites

http://www.ifcc.org/
https://www.eflm.eu/

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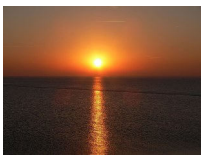
AI and Machine Learning uptake has been relatively slow in clinical labs but interest is developing. A status report from the AACC's Clinical Laboratory News plus an editorial and several papers in the October 2022 edition of CCLM discuss perceived benefits and outline related practicalities and ethical issues. The AACC report can be read here and the CCLM editorial here.

A podcast on the AACC's Laborastories section titled the AI Chatbot Story has a conversation between two experts in the AI field. They also co-authored a comprehensive review on the topic *(Rise of the Machines: Artificial Intelligence and the Clinical Laboratory)* in the Journal of Applied Laboratory Medicine (the AACC journal). Download free here.



Sunshine and Science: Rickets and the Discovery of Vitamin D

Dr. Martin Healy

Frederick Gowland Hopkins, the first professor of biochemistry at Cambridge University, made the original, observation that specific dietary components other than carbohydrates, proteins, and lipids were necessary for normal growth and development. He published his findings in the Journal of Physiology in 1912. He referred to these components as 'accessory factors'. Although there were numerous tantalising hints, as early as the 14th century, of connections between missing food factors and ill health, particularly beriberi and scurvy, these early observation were generally ignored at the time. Gowland is also credited with founding the field of clinical biochemistry and being the first to set nutrition on a firm scientific foundation. In 1929, he was jointly awarded the Nobel Prize in Physiology or Medicine "for his discovery of the growth-stimulating vitamins" along with Christiaan Eijkman "for his discovery of the antineuritic vitamin". There was some debate about the award because it was pointed out that other researchers had also made significant contributions.

How did 'vitamins' get their name? It was felt that Gowland Hopkins' use of the term "accessory factors" was too cumbersome. In 1913 the Polish biochemist, Casimir Funk, gave them the generic name 'vitamines', derived from the term 'vital amines', because he believed, mistakenly as it turned out, that all of the newly discovered factors contained an amine group. In 1920, Jack Drummond, a prominent UK biochemist and nutrition researcher at the time, suggested dropping the 'e' from 'vitamine' and adopting the convention of naming the vitamins using the letters of the alphabet. Hence, vitamins A,B,C, D, etc. This was eventually accepted internationally after some resistance. Drummond was instrumental in cementing the role of nutrition as a science and played a crucial role in co-ordinating the UK's response to food shortages during the Second World War. Sadly, Jack Drummond, his wife, and 10-year-old daughter were murdered in 1952 while holidaying in France. The case generated enormous media attention at the time. Although charges were brought against an individual, there has never been a satisfactory explanation of the motives behind the murders. More than one conspiracy theory has been suggested.

Rickets and Vitamin D: The consequences of vitamin D deficiency for bone pathology, particularly rickets in children and adolescents, have been recognised for millennia. However, vitamin D as an aetiological factor was only discovered in the 1920s. Rickets can be associated with bone pain, bone softening, short stature, bow legs, knock knees and dental deformities. The symtoms are the end products of chronic vitamin D deficiency, which results in a critical imbalance of calcium homeostasis and a lack of mineralisation of the epiphyseal plates, where normal bone growth takes place.

The works of two eminent Greek physicians from the second century AD who later practiced in Rome, Soranus of Ephesus and Galen, contain the earliest known references to a condition resembling rickets. They both emphasised the value of sunlight and maintaining a balanced diet as prophylactic measures and described the skeletal symptoms of rickets-like disease. With no means of dissemination, the advice gained little traction. According to archaeological data based on the examination of skeletal remains rickets was extremely common throughout prehistory and was especially prevalent during England's Industrial Revolution.

Comprehensive documented descriptions of rickets did not appear until the 17th century. The first was written in 1645 by Daniel Whistler for his MD thesis, a brief 8 pages, titled 'De morbo puerili Anglorum, quàm patrio sermone indigenæ vocant 'the Rickets' (literal translation: On the childish disease of the English, which the natives call in their native tongue 'the Rickets'). A significantly larger essay, running to several hundred pages and written primarily by Francis Glisson, followed in 1650. The first edition was titled 'De Rachitide' ('Of Rickets'). Whistler's reputation was somewhat tarnished after his death. He was accused of plagiarism, falsifying his dissertation date and embezzling money from the Royal Society although it has been suggested the accusations may have been encouraged by professional rivalry.

One hundred and seventy years later an important observation was made by Jędrzej Śniadecki, a Polish physician and chemist. He noted, in 1882, that children living in cramped, crowded conditions in Warsaw were far more susceptible to developing rickets compared to children living in the countryside. He speculated that the difference was the availability of ample direct sunlight in rural areas compared to the dark narrow streets of Warsaw. He was the first to suggest such a link. Theobald Palm, a British medical missionary, while based in Japan, noticed the almost complete absence of rickets in the young population. When he returned to England, however, he saw that rickets was endemic there. He collected evidence from missionary colleagues for several European countries and concluded that the prevalence of rickets was latitude-dependent. Less year round sunshine at higher latitudes equated with more rickets. He published his findings in 1890. Both Sniadecki's and Palm's findings were more or less ignored at the time. Their findings were dismissed as observational only with no proof. It took almost 100 years from Sniadecki's report in 1822 to provide proof. In 1919 Kurt Huldschinski, a German paediatrician, showed for the first time that shining artificially generated UV light on the skin of children cured rickets. He demonstrated, also, that exposing just one arm to the light resulted in a body-wide cure demonstrating the effect was systemic.

Diet and rickets: Fish oils as health remedies were recorded in the writings of Hippocrates in the 5th century BC and Pliny the Elder in the 2nd century AD (he died during the eruption of Vesuvius in 79 AD). Cod liver oil, as a food, emerged in the Viking era (700-1100 AD). It was used as a folk remedy for several centuries in Northern Europe. Its earliest recorded use as a medication dates back to 1789 and is attributed to Dr. Robert Darbey in Manchester Infirmary who prescribed it for rheumatism. Anecdotal reports in the early 19th century mentioned the oil as a treatment for rheumatism and gout. Its first documented use to treat rickets was recorded by the German physician Dr. D Schutte in 1824. From here its use spread to other European countries. In the 1860s Armand Trousseau (also known for his Trousseau's sign for

hypocalcaemia and tetany) introduced its use into France. Over the following 40 years, there were intermittent reports of its use as an anti-rachitic medication. Many medical professionals of the day, however, were reluctant to accept that cod liver oil, as a simple nutrient, had medicinal properties. Interest in it waned in the scientific community until the early 20th century. A resurgence in scientific interest resulted from the identification of Gowland Hopkins' 'accessory factors' or vitamins, as they are now known, in food.

It fell to Edward Mellanby to scientifically prove the efficacy of cod liver oil in curing rickets, and Elmer Vernon McCollum to identify the component in the oil responsible. Former Gowland Hopkins student Mellanby conducted a complex set of dietary studies on Beagle puppies over a five-year period in London. By fortuitously keeping the dogs indoors, he was able to demonstrate definitively that cod liver oil had a substance that could treat rickets even in the absence of sunshine. He found it to be a lipid-soluble chemical, but erroneously believed it to be fat soluble A, identified a few years earlier. His findings were published in 1919 and convinced sceptics that rickets was the outcome of a specific nutritional deficiency. Unrelated to his work on nutrition, Mellanby, in his role as Secretary of the Medical Research Council, was responsible for bringing Howard Florey to Oxford University to work on the extraction and purification of penicillin, which to date has saved an estimated 200 million lives.

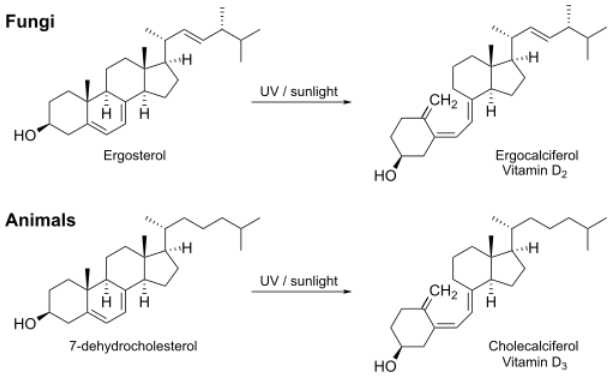
Elmer McCollum initially worked in the Agricultural Research Department, in the University of Wisconsin. He claimed to have discovered fat soluble A in 1913 (mentioned above) which was later renamed vitamin A, the first 'accessory factor' to be identified. The claim, however, has been disputed. He is credited with using rat colonies for the first time in nutrition intervention studies which greatly simplified dietetic research. He left Wisconsin in 1917 to take up a position in John Hopkins University. His departure from Wisconsin proved to be controversial. It was alleged that he took many of his colleagues lab notebooks with him and published uncredited articles based on their content. There is also speculation that he released all of the lab rats in the Wisconsin lab before he left, setting back research by months. In 1922 he showed that Mellanby's food factor in cod liver oil was not fat soluble A but a new compound he called fat soluble D (later vitamin D). He went on to become a major figure in nutrition research and development in the US. His rule was "Eat what you want after you have eaten what you should."

Joining the dots: In 1919 Harriette Chick, while working at the Lister Institute in London, travelled to Vienna with several colleagues to investigate the extremely high prevalence of rickets there. She was aware of the effects of both cod liver oil and sunlight on rickets and, after a series of studies, proved that cod liver oil and sunlight, used separately or in combination, cured rickets. She published her findings in 1922. With a distinguished career in nutrition she was a founder member of the Nutrition Society in 1941 and appointed Dame of the British Empire in 1949. She died in 1977 at the age of 102, having witnessed many new developments in the physiology of vitamin D.

The studies of Chick and Mellanby in the 1920s accelerated efforts to understand the connections between vitamin D and light. In 1916 Harry Steenbock (a then student of McCollum in Wisconsin), noted that the calcium status of goats was better when they were kept outdoors rather than confined indoors. In 1924 Steenbock, after McCollum departed to Princeton and with new information available to him, made the conceptual leap to irradiate both rats and/or their food with artificial UV light. He found, in both cases, that irradiation could prevent or cure experimental rickets. Further work led him to conclude that an inactive lipid-soluble factor in skin and food was being converted by exposure to UV light to an active anti-rachitic agent, vitamin D. This was considered groundbreaking at the time. Irradiation of food revolutionized the treatment of rickets. Steenbock went on to patent the idea of irradiating foods, particularly milk, and set up a foundation in Wisconsin to benefit nutrition research and development using revenues generated. He refused to benefit personally from the patents but was eventually coerced by the foundation into taking 15% of funds raised. Having established that Vitamin D could be produced in both food and skin the logical next step was to isolate and determine its chemical structure.

Structure of vitamin D: In 1925, laboratories in New York, London, and Göttingen started a collaboration to identify the chemical structure vitamin D2 (ergocalciferol), isolated from ergot fungi. Its structure was eventually determined in 1931 by Adolf Windaus, a German chemist and Nobel Prize co-recipient for Chemistry in 1929 for his work on cholesterol and sterols, and Frederick A. Askew (National Institute for Medical Research London). In 1936, Windaus also determined the chemical structure of vitamin D3 (cholecalciferol) found in all vertebrates. He also identified its parent compound, 7-dehydrocholesterol (7DHC), in skin. UV light is absorbed by 7DHC in the epidermis and a cascade is initiated resulting in vitamin D3 formation.

It would be another 30 years before further major developments in understanding the physiology of vitamin D took place.



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